

Impaired systemic oxygen extraction in treated exercise pulmonary hypertension: a new engine in an old car?

Mariana Faria-Urbina^{1,2}, Rudolf K.F. Oliveira^{1,2,3}, Sergio A. Segrera^{1,2}, Laurie Lawler^{1,2}, Aaron B. Waxman^{1,2} and David M. Systrom^{1,2}

¹Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; ²Heart & Vascular Center, Brigham and Women's Hospital, Boston, MA, USA; ³Division of Respiratory Diseases, Department of Medicine, Federal University of São Paulo (UNIFESP), São Paulo, SP, Brazil

Abstract

Ambrisentan in 22 patients with pulmonary hypertension diagnosed during exercise (ePH) improved pulmonary hemodynamics; however, there was only a trend toward increased maximum oxygen uptake (VO_2max) secondary to decreased maximum exercise systemic oxygen extraction (Ca-vO_2). We speculate that improved pulmonary hemodynamics at maximum exercise “unmasked” a pre-existing skeletal muscle abnormality.

Keywords

systemic oxygen extraction, pulmonary hypertension, ambrisentan, exercise

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Pulmonary hypertension diagnosed during exercise (ePH) is increasingly recognized as a clinically relevant and early form of pulmonary arterial hypertension (PAH);¹ however, ePH is not universally accepted as a disease worthy of diagnosis or treatment.^{2,3} Our group has recently completed an open label study of the safety and efficacy of ambrisentan in patients with ePH,⁴ showing that despite improvement in pulmonary hemodynamics and functional status, there was only a trend toward increased maximum oxygen uptake (VO_2max). In the present report, we aimed to explain this discrepancy by examining the Fick principle determinants of VO_2max of 22 patients evaluated in the aforementioned clinical trial.

The study was approved by Partners Human Research Committee, as previously reported.⁴ ePH was defined as mean pulmonary artery pressure (mPAP) > 30 mmHg, pulmonary arterial wedge pressure (PAWP) < 20 mmHg, and pulmonary vascular resistance (PVR) > 1 Wood Units (WU) at peak exercise, in the absence of resting PAH.¹ All participants underwent invasive cardiopulmonary exercise

testing at baseline and at six-month follow-up.⁴ In the present report, we analyzed cardiac output (CO), systemic oxygen extraction (Ca-vO_2), and delivery (DO_2) based on Fick principle determinants of VO_2max . In an effort to adjust for anemia (a known side effect of ambrisentan),⁵ peak Ca-vO_2 was corrected for hemoglobin (Hb) levels. Data are presented as n, n (%) or mean \pm standard deviation. The distribution of continuous variables was evaluated using Shapiro–Wilk test. Comparisons between parameters obtained at baseline and during follow-up were performed using paired t test or Wilcoxon signed-rank test, as appropriate for distribution. $P < 0.05$ was considered statistically significant. The statistical analyses were performed using SPSS software, Version 19 (IBM Company,

Corresponding author:

David M. Systrom, Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Clinics 3, 75 Francis Street, Boston, MA 02115, USA.

Email: dsystrom@partners.org



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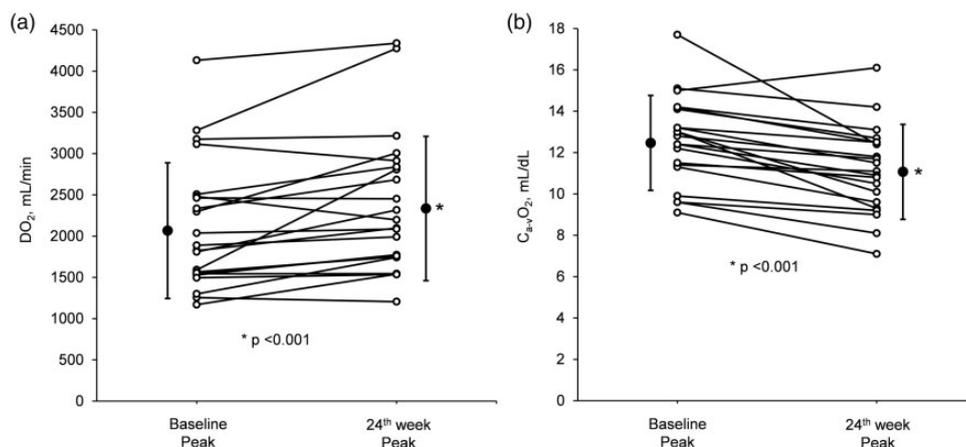


Fig. 1. (a) Oxygen delivery (DO₂) and (b) oxygen extraction (Ca-vO₂) at peak exercise.

Armonk, NY, USA) and Stata 14 (Stata Corp LP, College Station, TX, USA).

Of the 30 enrolled patients, 22 completed the study protocol. Eight individuals were excluded from the study due to adverse side effects, as previously described.⁴ The mean age was 58.6 ± 9.9 years (8 men, 14 women). At 24 weeks and at peak exercise, there was reduction of mPAP and PVR while CO was improved. Peak systemic vascular resistance (SVR) was decreased. While there was improvement in peak DO₂ (Fig. 1), there was only a trend toward increased VO₂max % predicted. No difference in VO₂ at the anaerobic threshold (% VO₂max predicted) (baseline = 45.0 ± 14.1%, 24 weeks = 47.5 ± 16.2%; *P* = 0.36) or maximum work rate was observed. Peak Ca-vO₂ (Fig. 1), Hb (baseline = 14.0 ± 1.3 g/dL, 24 weeks = 13.4 ± 1.7 g/dL; *P* = 0.005), and arterial oxygen content (CaO₂) were decreased. After Ca-vO₂ was corrected for Hb, it remained lower compared to the baseline value. There was no difference in maximum exercise arterial pH, arterial carbon dioxide partial pressure, arterial oxygen partial pressure (PaO₂), arterial oxygen saturation (SaO₂), alveolar-arterial oxygen tension difference, mixed-venous pH, mixed-venous carbon dioxide partial pressure, and mixed-venous oxygen partial pressure, while mixed-venous oxygen saturation was increased at follow up (Table 1).

A sub-analysis of eight patients with parenchymal lung disease did not demonstrate a deleterious effect on PaO₂ (baseline = 70.1 ± 18.2 mmHg, 24 weeks = 69.7 ± 18.3 mmHg; *P* = 0.88) and/or SaO₂ (baseline = 91.6 ± 3.8%, 24 weeks = 91.5 ± 4.2%; *P* = 0.86). No treatment-related changes of pulse oxygen saturation after 6-min walk test were observed in the eight patients with parenchymal lung disease (baseline = 91.88 ± 5.25%, 24 weeks = 90.67 ± 3.72%; *P* = 0.08).

The principal finding of the current report is that maximum exercise Ca-vO₂ decreased in ePH patients treated with ambrisentan, blunting a potential rise in VO₂max due to improved pulmonary hemodynamics and DO₂. This may be important for clinical trial design in pulmonary vascular

Table 1. Peak exercise hemodynamics and gas-exchange variables.

	Baseline	Week 24	<i>P</i>
mPAP (mmHg)	38.0 ± 6.6	33 ± 5.2	0.001
PVR (WU)	2.3 ± 0.9	1.4 ± 0.5	0.0002
CO (L/min)	10.9 ± 3.8	13.2 ± 3.8	0.0001
SVR (dynes/s/cm ⁻⁵)	836.7 ± 241.8	649.4 ± 200.1	0.0001
DO ₂ (mL/min)	2075 ± 823	2344 ± 875	<0.001
VO ₂ max (% predicted)	75.0 ± 19.3	79.4 ± 21.4	0.07
VO ₂ max (mL/min)	1430 ± 549.99	1512 ± 615.15	0.03
WR (watts)	109.4 ± 65.50	111.7 ± 58.67	0.68
Ca-vO ₂ (mL/dL)	12.5 ± 2.3	11.1 ± 2.3	0.0001
Ca-vO ₂ /Hb (mL/dL)	0.89 ± 0.12	0.83 ± 0.15	0.003
CaO ₂ (mL/dL)	18.7 ± 2.4	17.4 ± 2.6	<0.001
pH	7.37 ± 0.04	7.36 ± 0.05	0.38
PaCO ₂ (mmHg)	34.1 ± 4.4	34.4 ± 5.9	0.81
PaO ₂ (mmHg)	82.8 ± 18.5	79.4 ± 16.8	0.15
SaO ₂ (%)	94 ± 3	94 ± 4	0.39
P _{A-a} O ₂ (mmHg)	34.7 ± 16.0	36.7 ± 14.3	0.53
pHv	7.26 ± 0.05	7.26 ± 0.05	0.55
PvCO ₂ (mmHg)	58.7 ± 7.6	57.6 ± 6.9	0.38
PvO ₂ (mmHg)	25.5 ± 3.4	26.4 ± 3.3	0.25
SvO ₂ (%)	33 ± 8	36 ± 8	0.04

Data are presented as n, mean ± standard deviation.

mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; CO, cardiac output; SVR, systemic vascular resistance; DO₂, oxygen delivery; VO₂, oxygen uptake; WR, work rate; Ca-vO₂, systemic oxygen extraction; Hb, hemoglobin; CaO₂, arterial oxygen content; PaCO₂, arterial carbon dioxide partial pressure; PaO₂, arterial oxygen partial pressure; SaO₂, arterial oxygen saturation; P_{A-a}O₂, alveolar-arterial oxygen tension difference; pHv, mixed-venous pH; PvCO₂, mixed-venous carbon dioxide partial pressure; PvO₂, mixed-venous oxygen partial pressure; SvO₂, mixed-venous oxygen saturation.

disease. If the endpoint of the clinical trial is a non-invasive VO₂max alone, improvements in exercise pulmonary hemodynamics may be masked by the confounding effects of impaired Ca-vO₂.

One possible explanation for our observations is the presence of systemic arteriolar endothelial dysfunction in ePH that is unmasked by its treatment. Systemic arterial endothelial dysfunction may exist in PAH due to a deficit of vasodilators such as nitric oxide and prostacyclin, and overexpression of vasoconstrictors, such as thromboxane A2 and endothelin-1.⁶ In the human, Peled et al.⁷ evaluated endothelial dysfunction, reporting lower post occlusion brachial artery flow-mediated dilation in PAH patients when compared to healthy controls. During exercise, under normal circumstances, regional blood supply to skeletal muscle is progressively shifted away from other organ beds such as the gut and kidney toward exercising muscle and within the muscle toward oxidative fibers.⁸ Increased plasma endothelin-1 during exercise may contribute to such redistribution of blood flow.^{9,10} In the rat, the arteriolar resistors serving fast-twitch glycolytic skeletal muscle fibers are endothelin-1 sensitive,¹¹ so it is possible their blockade by ambrisentan allows disproportionate perfusion of fast-twitch glycolytic fibers, depriving slow-twitch muscle fibers and their mitochondria of blood flow and DO₂. This is a critical observation, since slow-twitch fibers have a greater influence on VO₂max when compared with fast-twitch fibers.¹² In the hypoxic rat, skeletal muscle capillary blood flow is increased by ambrisentan.¹³ In another study, bosentan increased flow mediated vasodilation in PAH.¹⁴ Our data suggest that if ET-1 blockade increases skeletal muscle blood flow at peak exercise in PAH, it does so indiscriminately, without preferential perfusion of the slow-twitch oxidative muscle fiber. Furthermore, the lowered SVR after treatment with ambrisentan suggests that inappropriate systemic vasodilation secondary to the drug might have adversely affected muscle oxygen uptake and utilization.

Abnormal systemic microcirculatory structure may also underlie our observations. Lower capillary density within the skeletal muscle impairs muscle DO₂, despite normal CO response and estimated DO₂ in PAH.¹⁵ Potus et al.¹⁶ suggested skeletal muscle microvessel loss associated with downregulation of microRNA-126 correlates with poor exercise tolerance in PAH. In a manner similar to systemic arteriolar endothelial dysfunction, changes in vessel structure combined with drug-induced increased blood flow to the limb skeletal muscle, may result in mismatch of perfusion and oxidative metabolism, and impaired Ca-vO₂.

It is also possible that intrinsic abnormality of skeletal muscle mitochondrion exists in PAH and is unmasked after its treatment with ambrisentan. The hallmark of a mitochondrial myopathy in the human is impaired Ca-vO₂ at peak exercise.¹⁷ Previous studies have shown that impaired exercise capacity in PAH is related to the presence of cellular signaling networks that prompt muscle proteolysis and downregulate protein synthesis, and low expression of proteins that regulate mitochondrial fusion in skeletal muscle, an important contributing factor to skeletal muscle atrophy and excitation-contraction impairment in patients with PAH.¹⁸ Malenfant et al. studied the proteomic signature

of skeletal muscle in PAH and demonstrated downregulation of proteins related to mitochondrial structure and function, with lower expression of oxidative enzymes and higher expression of glycolytic enzymes in PAH.¹⁹ Therefore, it is possible that intrinsic mitochondrial dysfunction is associated with impaired Ca-vO₂ in our population and is exaggerated when DO₂ is improved due to therapy.

Recently, the ERS statement in pulmonary hemodynamics during exercise²⁰ defined ePH by the presence of mPAP < 25 mmHg at rest and >30 mmHg at peak exercise, and total pulmonary resistance (TPR) > 3 WU. In a similar way, our definition includes indices of pressure and resistance and, therefore, we do not think the implementation of the ERS definition to our population would have changed our results.

In conclusion, we speculate that improved pulmonary hemodynamics and CO at maximum exercise “unmasked” a pre-existing skeletal muscle abnormality, which could include systemic vascular and/or mitochondrial structure or function. We suggest the following analogy: if improved DO₂ after ambrisentan is a “new engine,” and the peripheral problem is the “old car;” placing a “new engine in an old car” would allow us to find the other parts of the car that do not work properly.

Our observations are limited by the small number of patients and the single-center design of the clinical trial. Also, the analysis was restricted to the per-protocol population and, therefore, can lead to biased results that favored inclusion of patients whose pulmonary hemodynamics improved. However, this is the first study, to our knowledge, to describe impaired exercise Ca-vO₂ after treatment of ePH with a pulmonary vasodilator. Impairment or unmasking of abnormal Ca-vO₂ during exercise may contribute to exertional intolerance in ePH and may represent a confounding variable for clinical trials whose outcomes include the functional status of the patient. Multicenter placebo-controlled randomized clinical trials are warranted to confirm our findings in ePH and document the influence of pulmonary vasodilators on exercise capacity, including VO₂max and its Fick principle determinants.

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Conflict of interest

The author(s) declare that there is no conflict of interest.

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